User Performance of the CONTOUR® NEXT and CONTOUR TV3 Blood Glucose Monitoring Systems

Protocol GCA-PRO-2018-006-01

NCT03730480

Sponsor: Ascensia Diabetes Care
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I have read this protocol and agree to conduct the study as outlined. I also agree that prior to seeking approval from an Institutional Review Board (IRB), the Ascensia Diabetes Care study manager must approve any changes to the protocol.

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List of Abbreviations

AE	Adverse Event
AST	Alternative site test
BG	Blood Glucose
BGM	Blood Glucose Meter
BGMS	Blood Glucose Monitoring System
CCRA	Certified Clinical Research Associate
CLSI	Clinical and Laboratory Standards Institute
CSR	Clinical Study Report
EDC	Electronic Data Capture
FDA SMBG: 2016	Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use, Guidance for Industry and Food and Drug Administration Staff. Issued 11Oct2016, Food and Drug Administration, USA.
ICF	Informed Consent Form
IRB	Institutional Review Board
ISO 15197:2013 (and EN ISO 15197:2015)	In vitro diagnostic test systems – Requirements for blood–glucose monitoring systems for self-testing in managing diabetes mellitus. Issued 15May2013, International Organization for Standardization, Switzerland. **Note:** All references to ISO:15197:2013 in this protocol also encompass EN ISO 15197:2015.
PI	Principal Investigator
QRG	Quick Reference Guide
SMBG	Self-Monitoring of Blood Glucose
UADE	Unanticipated Adverse Device Effect
UG	User Guide
YSI	YSI Glucose Analyzer™ (YSI Life Sciences, Yellow Springs, OH)

1.0 Background Information

CONTOUR® NEXT is the proposed name of a blood glucose monitoring system (BGMS) consisting of a new meter and marketed CONTOUR NEXT® test strip. The development name of the meter is LIGHTNING NEXT. CONTOUR TV3 is the proposed name of a BGMS consisting of a new meter and new V3 test strips. The development name of the meter is THUNDER TV3. The meters can wirelessly transmit BG results using Bluetooth Low Energy to the CONTOUR mobile application that will be available on specified versions of the iOS and Android mobile platforms.

This clinical trial will assess the performance (accuracy) of the CONTOUR NEXT and CONTOUR TV3 meters by lay users enrolled as subjects in the study, and by health care professionals (also called study staff). The trial will follow the requirements and procedures described in FDA Guidance on Self-monitoring Blood Glucose Test Systems: 2016 (FDA SMBG:2016) [1] and ISO 15197:2013 International Standard, Section 8[2]. Results will be evaluated and reported for each of the two BGMS according to each of the two standards (FDA and ISO), for a total of four reports. CONTOUR NEXT results and CONTOUR TV3 results will not be compared to one another.

2.0 Study Objectives

Study objectives 2.1 and 2.2 are in accordance with **FDA SMBG: 2016**, Section C. Method Comparison / User Evaluation, and apply to data collected from **all subjects**: people with diabetes and a smaller number of naïve users (defined as people without diabetes). The objectives apply to both CONTOUR NEXT and CONTOUR TV3 BGMS, and the results from the two meter systems will not be compared to each other.

2.1 Primary Objective (FDA SMBG: 2016), all subjects:

2.1.1 Fingerstick Test: Obtain BGMS performance data in the hands of **lay users with diabetes and naïve users** (without diabetes) from fingerstick capillary blood using Microlet NEXT® lancing device.

- **95% of glucose results shall fall within ±15% of laboratory method across the entire tested range**
- **99% of glucose results shall fall within ±20% of laboratory method across the entire tested range**

2.1.2 Samples will adequately span the claimed measuring range. At least ten unaltered samples with blood glucose concentration at the lower limits of the measuring range (less than 80 mg/dl) and at least ten unaltered samples at the upper limit measuring range (greater than 250 mg/dl) will be obtained for each anatomical site (i.e. fingerstick & palm).

[1] Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use, Guidance for Industry and Food and Drug Administration Staff. Issued 11Oct2016, Food and Drug Administration, USA. (abbreviated FDA SMBG:2016)

[2] In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. Issued 15 May2013, International Organization for Standardization, Switzerland. (abbreviated ISO 15197:2013)

2.2 Secondary Objectives (FDA SMBG: 2016), all subjects:

2.2.1 Alternative Site Test (AST): Obtain BGMS performance data in the hands of **lay users with diabetes and naïve users** (without diabetes) from the palm site using the Microlet NEXT lancing device with the AST endcap. Acceptance criteria will be the same as fingerstick 2.1.1.

2.2.2 Subject Questionnaire 1: The questionnaire will include statements about the BGMS instructions for use (product labeling) and ease of use of the basic blood testing operations of the meter system. These statements will be given a rating by all of the subjects (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree), and frequency distributions will be tabulated. Results will be compared to the following criteria:

- **Acceptance criteria: At least 90% of the applicable statement responses from the questionnaire must be ≥ 3 to pass*.**

Study objectives 2.3.1 and 2.3.4 below are in accordance with **ISO 15197:2013, Section 8**, and apply to data collected ONLY from **subjects who have diabetes**. Objectives 2.3.2 and 2.3.3 also apply to subjects who have diabetes. The objectives apply to both CONTOUR NEXT and CONTOUR TV3 BGMS, and the results from the two meter systems will not be compared to each other.

2.3 Secondary Objectives, only subjects with diabetes:

2.3.1 Fingerstick Test: Obtain BGMS performance data in the hands of lay users with diabetes using fingerstick capillary blood obtained with Microlet NEXT lancing device.

- **95% of glucose results shall fall within ±15mg/dL of laboratory method at glucose concentration <100 mg/dL and within ±15% at glucose concentrations ≥100 mg/dL**

2.3.2 Alternative Site Test (AST): Obtain BGMS performance data in the hands of lay users with diabetes using capillary blood from the palm site obtained with Microlet NEXT lancing device with the AST endcap. Acceptance criteria will be the same as fingerstick 2.3.1.

2.3.3 Venous Blood Test: Obtain BGMS performance data using venous blood from lay users with diabetes. Acceptance criteria will be the same as fingerstick 2.3.1.

2.3.4 Subject Questionnaire 1: The questionnaire will include statements about the BGMS instructions for use (product labeling) and ease of use of the basic blood testing operations of the meter system. These statements will be given a rating by the subjects with diabetes (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree), and frequency distributions will be tabulated. Results will be compared to the following criteria:

*This is a "total population" (hypothesis test) requirement for the pool of all subjects.

- **Acceptance criteria: There must be at least a 90% probability that a user would respond with a score of 3 or higher to statements concerning instructions for use or ease of use.**[**]**

Study objectives 2.4 below are internal objectives and apply to data collected from all subjects OR subjects who have diabetes, as specified for each objective. The objectives apply to CONTOUR NEXT and CONTOUR TV3 BGMS as noted, and the results from the two meter systems will not be compared to each other.

2.4 Secondary Objectives **(internal objectives)**:

2.4.1 Fingerstick Test **(only subjects with diabetes)**: Obtain BGMS performance data in the hands of lay users with diabetes using fingerstick capillary blood obtained with Microlet NEXT lancing device.

CONTOUR NEXT:

- **95% of glucose results shall fall within ±10.5mg/dL of laboratory method at glucose concentrations <100 mg/dL and within ±10.5% at glucose concentrations ≥100 mg/dL**[**]**

CONTOUR TV3:

- **95% of glucose results shall fall within ±12.5mg/dL of laboratory method at glucose concentrations <100 mg/dL and within ±12.5% at glucose concentrations ≥100 mg/dL**[**]**

2.4.2 Study staff test **(both BGMS; two analyses, one for all subjects and one for only subjects with diabetes)**: Obtain BGMS performance data in the hands of trained study staff testing subjects' fingerstick blood obtained with Microlet NEXT lancing device.

- **95% of glucose results shall fall within ±15mg/dL of laboratory method at glucose concentrations <100 mg/dL and within ±15% at glucose concentrations ≥100 mg/dL**[*,**]**

2.4.3 Subject Questionnaire 2 **(both BGMS; only subjects with diabetes)**: This questionnaire for subjects with diabetes will include statements about user preferences and feedback regarding the features of the BGMS in routine diabetes management. These statements will be given a rating by the subjects (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree), and frequency distributions will be tabulated.

- **Acceptance criteria: There are no pass/fail criteria for Questionnaire 2.**

[**]This is a "total population" (hypothesis test) requirement for the pool of all subjects with diabetes.

3.0 Study Design Summary

This study was designed to satisfy both the ***FDA SMBG:2016*** and the ***ISO 15197:2013, Section 8*** requirements. Besides different analysis criteria, the main difference between these regulations is that FDA SMBG:2016 requires that both naïve users (people without diabetes) and people with diabetes are included in the study population. The ISO 15197:2013 standard states that the study population shall be people with diabetes.

The study will be conducted at two clinical sites and enroll a total of approximately 370 lay users. Ten to fifteen percent (10 - 15%) of the enrolled subjects will be people without diabetes and the remaining subjects will be people with diabetes.

For this study, there must be at least 350 total evaluable fingerstick self-test results and at least 350 total evaluable AST palm self-test results for each BGMS, CONTOUR NEXT and CONTOUR TV3. In addition, per FDA SMBG:2016, at least 10 unaltered fingerstick blood samples will be < 80 mg/dL and 10 will be > 250 mg/dL. Subject enrollment will continue until the required evaluable samples are collected.

Sites are not required to replace subjects with diabetes who did not have evaluable venous blood results.

The subjects will be 18 years and older. Each subject will make one visit, lasting approximately 2 hours, to the clinical trial site. Study sessions will be conducted by study staff members who have been trained on all aspects of the protocol, forms, the use of the CONTOUR NEXT and CONTOUR TV3 systems, data collection, and GCP.

All subjects will complete the informed consent process before performing any study procedures.

Procedures - All Subjects

According to a randomization schedule, subjects will be assigned to: 1) use either the CONTOUR NEXT or CONTOUR TV3 meter first, and 2) use one of three test strip lots corresponding to each meter throughout the visit.

The untrained subjects, who have never used either of the systems previously, will be sequestered in such a way that they cannot observe or be influenced by the testing technique of other study participants. They will learn to use the assigned meter by reading the corresponding User Guide (UG) and Quick Reference Guide (QRG). Each subject will perform one fingerstick self-test using a Microlet NEXT or similar lancing device and the assigned meter. Immediately following the subject self-test, a Tenderlett™ or similar device will be used by the study staff on the subject's finger (same hand) to collect a capillary sample for testing on the YSI Glucose Analyzer.

Immediately following the Tenderlett lancing, subjects will lance their palm using the Microlet NEXT lancing device (with AST clear endcap) and will perform a self-test using the meter.

Immediately following the AST test, the staff person will perform a fingerstick test on the subject. All subject self-test results and study staff results will be compared to YSI results from blood obtained from the Tenderlett fingerstick.

Hematocrit will be measured for all subjects.

All Subjects will then complete a questionnaire (Questionnaire 1) to provide feedback on the meter system and instructions for use (UG and QRG).

Procedures - Only Subjects with Diabetes

Subjects with diabetes will be given a venipuncture. The venous blood will be tested by the study staff using the CONTOUR NEXT and CONTOUR TV3 systems, maintaining randomized first meter order, and the YSI lab analyzer. The venipuncture may be performed any time after the subject is enrolled (i.e. completed informed consent and passed inclusion/exclusion criteria).

After all testing is completed, staff will demonstrate to the subjects with diabetes several features of the meter system that would not necessarily be experienced during the brief accuracy testing. These subjects will be given a second questionnaire (Questionnaire 2) to provide feedback about the new features of the system.

Procedures repeated with second BGMS

After completing study procedures for one BGMS, subjects will then repeat all of these procedures using the second BGMS, except the hematocrit and venipuncture procedures. (Hematocrit is measured on a separate instrument and is not meter-specific; venipuncture is performed once and measured on both meters, as previously described.)

4.0 Subject Recruitment, Inclusion/Exclusion Criteria

Subject Recruitment: At least 370 subjects will be enrolled into the study. These will be people with diabetes (type 1 or type 2) and a smaller number, 10 - 15%, without diabetes. The subjects will be members of the local communities.

4.1 Inclusion Criteria:

4.1.1 Males and females, 18 years of age and older

4.1.2 Ability to speak, read and understand English. Subjects must demonstrate ability to read a paragraph from the first page of the UG to qualify for the study.

4.1.3 Willing to complete all study procedures

4.2 Exclusion Criteria:

4.2.1 Hemophilia or any other bleeding disorder

4.2.2 Pregnancy (self-reported)

4.2.3 Physical, visual or neurological impairments that would make the person unable to perform testing with the BGMS.

4.2.4 Previous participation in a blood glucose monitoring study using the Ascensia CONTOUR NEXT or CONTOUR TV3 BGMS.

4.2.5 Working for a medical laboratory, hospital or other clinical setting that involves training on or clinical use of blood glucose monitors.

4.2.6 Working for a competitive medical device company, or having an immediate family member or someone who is not a family member but is living within the household of someone who works for such a company.

- Immediate family members are the subject's parents, spouse, children, and siblings, including the parent's spouse; step-children and adopted children and their spouses.
- A competitive medical device company is a company that provides a medical device or components of a device that is related to diabetes.

For example, people who are not eligible are those who work for companies that create or manufacture the following (or a company that is in a partnership with a company that provides such devices): lancing devices, blood glucose monitoring systems, continuous glucose monitoring systems, insulin pens, or systems related to the measurement of HbA1c.

People who are eligible are those who work for companies associated with products such as wound dressings, medications or dietary products.

4.2.7 A condition, which in the opinion of the investigator or designee, would put the person or study conduct at risk. The reason for exclusion will be clearly documented by investigator or designee on the subject disposition form.

4.3 General Enrollment Details - Combined across sites

4.3.1 The following additional population criteria are study goals with each site recruiting to meet these goals:

1. At least 70% of subjects will be younger than age 65.
2. Ten to fifteen % (10-15%) of subjects will be people without diabetes.
3. At least 20% of subjects (with diabetes) will have type 1 diabetes.

4.3.2 No laboratory tests (e.g., pregnancy) are required to assure qualification. Subjects' verbal responses will be accepted and recorded on forms which will serve as source documents for the electronic data capture (EDC) system.

4.3.3 Subject venipuncture may be performed at any time during the subject visit.

5.0 Materials and Methods

5.1 Resources Supplied by Investigational Site

5.1.1 **Staffing**

1. Principal Investigator and, as needed, Sub-Investigator(s)
2. Study Coordinator

3. Two or more study staff to conduct the study
4. Staff person(s) to measure hematocrit, prepare samples for YSI analysis, and perform YSI analysis of venous and capillary blood (plasma) and serum controls (per site: sponsor agreement)
5. Data entry person for EDC data entry (Note: This requires EDC training.)

5.1.2 **Other**

1. Final informed consent forms (ICF), and other necessary supporting documents, as appropriate
2. Computer with internet connection for site and monitor access to EDC system
3. Facility with adequate space for conducting all testing. Site facilities for conducting subject visits must allow sufficient privacy so subjects cannot observe other subjects' BGMS testing procedures. Testing area must also be conducive to allowing subjects to focus on testing (i.e. background distraction to be kept to a minimum).
4. YSI analyzers, reagents, and supplies
5. Supplies to treat any hypoglycemic events
6. Venipuncture supplies
7. Laboratory supplies including: disposable pipets, gloves, alcohol wipes, band aids, gauze, parafilm, disposable benchtop covers
8. Tenderlett™ or similar single-use lancing device
9. Micro collection tubes with lithium heparin anticoagulant (no gel separator)
10. Hand warmers
11. Biohazardous bags and sharps containers

5.2 <u>Resources Supplied by Ascensia</u>

5.2.1 **Staffing**

1. Ascensia Study Manager
2. Study Monitor(s)

5.2.2 **Materials**

1. Protocol, EDC system, paper case report forms (CRF) and questionnaires, as needed
2. ICF template
3. CONTOUR NEXT meters (Note: Meters will have Bluetooth turned ON throughout the study.)
4. CONTOUR NEXT User Guides (UG) and Quick Reference Guides (QRG)
5. CONTOUR NEXT test strips - 3 lots labeled as RED, GREEN, BLUE (R, G, B). A minimum of 10 vials of test strips per lot will be provided.

6. CONTOUR TV3 meters (Note: Meters will have Bluetooth turned ON throughout the study.)
7. CONTOUR TV3 UGs and QRGs
8. V3 test strips – 3 lots labeled as RED, GREEN, BLUE (R, G, B). A minimum of 10 vials of test strips per lot will be provided.
9. CONTOUR NEXT/CONTOUR TV3 (Normal level) control solution
10. Microlet NEXT lancing device systems including clear, AST endcap. (All subjects will be provided new lancing devices and lancets; lancing devices will not be shared among subjects.)
11. Thermometer / hygrometer
12. Statspin™ microcentrifuge and tube rotors
13. Microhematocrit tube reader (or equivalent hematocrit measurement system), hematocrit rotors, sealant
14. Microhematocrit tubes without anticoagulant (for testing venous blood)
15. Microhematocrit tubes with anticoagulant (for testing capillary blood)
16. Clocks with 24-hr time option
17. Ascensia serum glucose traceability controls (four levels)
18. Disposable microtubes, disinfectant wipes for meters
19. Package delivery forms and envelopes (UPS or Fed Ex)

5.3 Site Staff Pre-Study Orientation

The Ascensia Study Manager, or designee, will review all study documents, procedures (including procedures for data collection and management), GCP, and usage of the CONTOUR NEXT and CONTOUR TV3 BGMS with the site staff. All site staff involved in subject testing sessions will successfully perform at least one control solution test with each of the two BGMSs. Study-specific EDC training will also be provided to study staff as necessary.

5.4 Safety and Disinfection Procedures:

1. Universal precautions will be used throughout the study.
2. Only study staff will perform disinfection procedures. Subjects will not perform disinfection.
3. A new CONTOUR NEXT and CONTOUR TV3 meter will be provided to each subject. At the end of the subject's visit, the meters will be disinfected and stored until they are returned to Ascensia.
4. A new Microlet NEXT or similar lancing device will be provided to each subject. At the end of the subject's visit, the lancing device will either be discarded or offered to the subject to take home.
5. The lancets used in the study (Tenderlett and Microlet lancets) will be disposed of in a biohazard sharps container after use.

6. Microlet lancets must be changed for each lancing by the subject. (Insert, remove, and discard into sharps container.)
7. Disposable exam gloves will be worn by site staff during study procedures where the risk of transmission of disease is present. These procedures include performing blood glucose measurements, sample processing, and laboratory procedures involving blood samples. A new pair of gloves will be used when working with each subject and will be changed between subjects.
8. All test strips are single-use and will be appropriately discarded after use.
9. Disposable bench top covers should cover the work area and must be changed between subjects.
10. A marketed BGM device may be used for determining the subject's glucose level during the study as needed for safety reasons or to ascertain the glucose level for study reasons. The meter will be disinfected after use with each subject.

5.5 Study Staff Quality Control Testing of Meters

Prior to enrollment of the first subject, the study staff will perform testing with Contour normal level control solution on all CONTOUR NEXT and CONTOUR TV3 meters. All staff control testing will be done out of sight of the study subjects. If the results are out of range, troubleshooting will be performed (see meter UGs) and the test will be repeated. If the meter tests are out of range after troubleshooting is complete, the meter will be removed from the study. This will be documented on the Problem Reporter form, as described in Section 5.15 'Device Problem Reporting'.

5.6 Subject Enrollment

5.6.1 At least 185 untrained subjects, who have never previously used the Ascensia CONTOUR NEXT or CONTOUR TV3 BGMS, should be enrolled into the study at each site in order to have a total of at least **350 evaluable fingerstick** and **350 evaluable AST palm** blood results for each BGMS. Of the fingerstick blood samples, 10 samples should be < 80 mg/dL and 10 samples > 250 mg/dL (by YSI assay). If this requirement is not achieved with 350 subjects, additional subjects should be enrolled to meet this fingerstick requirement. Note that the goal at each site should be approximately five capillary fingerstick blood results < 80 mg/dL and five > 250 mg/dL.

5.6.2 The site study staff will perform the following when the subject arrives at the clinical trial site:

1. Complete the informed consent process.
2. Assign a unique number to each subject.

5.6.3 The study staff will document subject demographics (including both screen-failed and enrolled subjects), diabetes history, medical conditions and medications information.

Subjects will also be asked when they last ate, took diabetes medications, and performed vigorous exercise.

5.6.4 If the subject does not have diabetes, the outside of the subject folder will be labeled to indicate that venipuncture should NOT be performed.

5.6.5 According to a randomization schedule, subjects will be assigned to: 1) use either the CONTOUR NEXT or CONTOUR TV3 meter first, and 2) use one of three test strip lots corresponding to the meter throughout the visit (lot R, B, or G).

5.7 Tests (See Table 5.2 for test scheme.)

Each subject will be provided with all the materials needed for self-testing during the visit: one CONTOUR NEXT meter, one CONTOUR TV3 meter, a Microlet NEXT or similar lancing device, lancets, Contour NEXT test strips, V3 test strips, CONTOUR NEXT and CONTOUR TV3 UGs and QRGs. The subject will be given time to review the UG and QRG to learn how to use the system but no training will be provided.

The subject will wash his/her hands thoroughly with warm water and soap, rinse and dry well.

5.7.1 **Fingerstick Testing**

1. The subject will perform a fingerstick using the Microlet NEXT lancing device and test his/her blood on Meter 1. The study staff person will record the time and test result of the successful meter test on the appropriate form. For instructions on handling error codes and repeat testing, refer to protocol section 5.10 'Errors'.
2. Immediately, but at least within 5 minutes of the fingerstick self-test, the study staff person will lance the subject's finger (preferably the same hand as above) with a Tenderlett device in order to collect enough blood for testing on the YSI Analyzer (approx. 200–300 uL). The time of this Tenderlett lancing will be recorded.
3. If adequate blood is not obtained from the Tenderlett lancing, 2 additional Tenderlett lancings are allowed (total of up to 3 Tenderlett lancings). The blood is to be combined into one tube for YSI analysis.
4. The blood sample will be centrifuged as soon as possible after sample collection but not longer than 15 minutes after the meter test. The study staff person will record the time of centrifugation.
5. In order to reduce glycolysis of the plasma, it is recommended that the plasma be transferred from the microtainer tube to a micro/dispo tube or similar container, prior to analysis on the YSI Analyzer.
6. The plasma sample will be assayed on the YSI Analyzer: 1 sip = 1 result from black probe and 1 result from white probe. See 5.12.3 for details on testing of plasma samples.

7. Immediately following the subject plasma sample, a serum control close to the level of the subject plasma will be tested. (No re-calibration is required). The serum control test result should be within the range shown in Table 5.1. See 5.12.3 for details.
8. Additional details regarding processing of blood samples for the YSI Analyzer are found in Appendix B.
9. If the time from meter test to blood centrifugation exceeds 15 minutes, the test is considered non-evaluable. This will not be considered a protocol deviation. Times of meter tests and centrifugation will be recorded.

5.7.2 **AST (palm) testing**

1. Only proceed to AST testing if an adequate blood sample is obtained from Tenderlett lancing for YSI analysis.
2. The same meter and test strip lot used for fingerstick testing will be used for AST testing.
3. Immediately following Step 5.7.1, the subject will perform an AST (palm) stick using the lancing device (new lancet), preferably on the same hand as the fingerstick lancing, and test his/her blood on Meter 1.
4. If adequate blood is not obtained from the Microlet palm lancings for the meter test, up to 2 additional Microlet palm lancings are allowed (total of up to 3 AST palm lancings).
5. The time of the successful AST meter test will be recorded. The time interval between the blood centrifugation and the AST meter test should be as soon as possible, and within 15 minutes or less.
6. If the time from meter test to blood centrifugation exceeds 15 minutes, the test is considered non-evaluable. This will not be considered a protocol deviation. Times of meter tests and centrifugation will be recorded.

5.7.3 **Study Staff test**

1. Immediately following the AST testing, the study staff person will perform a fingerstick lancing using the same Microlet lancing device (new lancet) on the subject, preferably on the same hand as the other fingerstick lancing.
2. The staff person will test the fingerstick blood using the same meter and test strip lot used by the subject.
3. The study staff will record the time of the meter test. The time interval between the blood centrifugation and the final staff meter test should be as soon as possible, and within 15 minutes or less.
4. If the time from meter test to blood centrifugation exceeds 15 minutes, the test is considered non-evaluable. This will not be considered a protocol deviation. Times of meter tests and centrifugation will be recorded.

5.8 Venous Blood Testing by Study Staff *(Only subjects with diabetes)*

5.8.1 The venipuncture and subsequent test may be performed at any time during the subject visit.

5.8.2 A venipuncture will be performed by a trained site phlebotomist. The subject's blood will be collected into one 4 mL heparin-coated Vacutainer tube.

5.8.3 The study staff person will place one drop of venous blood onto Parafilm®, then immediately perform one test with the same lot of test strips and the same meter used for capillary tests. Record the time of the successful venous meter test.

5.8.4 Refer to Section 5.10 for information on handling error codes and repeat testing.

5.8.5 The venous blood will be centrifuged as soon as possible after the meter test (within 15 minutes or less). Record the centrifugation time. If the time from meter test to blood centrifugation exceeds 15 minutes, the test is considered non-evaluable. This will not be considered a protocol deviation. Times of meter tests and centrifugation will be recorded.

5.8.6 Additional details regarding processing of blood samples for the YSI Analyzer are found in Appendix B.

5.8.7 The venous plasma sample will be assayed on the YSI Analyzer: 1 sip = 1 result from black probe and 1 result from white probe. See 5.12.3 for details on testing of plasma samples.

5.8.8 Up to three venipuncture attempts are allowed per subject, if subject and study staff agree, in order to obtain sufficient venous blood. If the venipuncture is ultimately unsuccessful, this will be recorded and will not be considered a protocol deviation.

5.9 **General**

5.9.1 All fingerstick and AST meter test results will be compared to the capillary YSI laboratory results.

5.9.2 All venous blood meter test results will be compared to the venous blood YSI laboratory results.

5.9.3 If adequate blood is not obtained from the subject or staff Microlet lancings, up to 2 additional lancings are allowed in each case (up to a total of 6 fingertip Microlet lancings).

5.9.4 If adequate blood is not obtained from the staff Tenderlett lancing, up to 2 additional lancings are allowed in each case (up to a total of 3 fingertip Tenderlett lancings).

5.9.5 If adequate blood is not obtained from the Microlet AST palm lancings, up to 2 additional palm lancings are allowed (total of up to 3 AST palm Microlet lancings).

5.9.6 If adequate blood is not obtained from the first venipuncture attempt, up to 2 additional attempts are allowed if subject and study staff agree (total of up to 3 venipuncture attempts).

5.9.7 **If the time from meter test to blood centrifugation exceeds 15 minutes, the test is considered non-evaluable.** This will not be considered a protocol deviation. Times of meter tests and centrifugation will be recorded.

5.9.8 Hand warmers may be used throughout the testing to increase blood flow.

5.9.9 It is preferred that all fingerstick and AST lancings are from the same hand if possible, for each meter.

5.9.10 Study staff will record all meter results on the appropriate form. If meters have turned off, meter memory will be reviewed and the results will be obtained from meter memory.

5.9.11 Study staff will record every instance of second chance sampling by checking the box provided on the CRF.

5.9.12 Study staff will record in the comments section of the meter testing form, any obvious testing errors by the subject or staff as appropriate for staff tests, and any abnormalities observed in the testing procedure or BGMS.

5.9.13 Note that once the fingerstick testing is started in 5.7.1, the subject should not eat, or use medications until the capillary/AST testing is completed in 5.7.2 to avoid changing glucose levels. The subject can eat/take medicines at any time to avoid or treat hypoglycemia or hyperglycemia. If the subject eats or takes medications, results obtained after eating or medicating will be non-evaluable.

5.10 Errors

5.10.1 If the meter reports an error code, the instructions shown in the UG should be followed. Re-testing is recommended (per the UG). No more than a total of 3 attempts are allowed.

5.10.2 If the subject feels that he/she made an error while testing, without any prompting from the study staff, he/she will repeat the test. The reason for the repeated test will be documented in the comments section of the form.

5.10.3 If the study staff feels that he/she made an error while performing staff fingerstick or venous testing, he/she will repeat the test. The reason for the repeated test will be documented in the comments section of the form.

5.10.4 The study staff will record all non-numeric codes - QNS (Quantity not sufficient), NO (Not obtainable), and meter error codes as appropriate for the meter tests.

5.11 Hematocrit

Two hematocrit tubes will be filled with either the subject's venous or capillary blood, and then centrifuged. The hematocrit will be measured from only one tube; the second tube will be collected as a backup in case the first tube is not measureable (i.e., tube spun out, broken tube, clay seal compromised, etc.). Subject hematocrit measurement should be within 0-70% in order for the subject BG results to be considered evaluable.

Note: Microhematocrit tubes with anticoagulant will be used for capillary blood hematocrit measurements collected directly off the fingertip and microhematocrit tubes without anticoagulant will be used for venous blood.

Additional details regarding hematocrit measurements are found in Appendix C.

5.12 YSI Glucose Analyzer

5.12.1 YSI Analyzer Operation and Control Tests

The YSI Glucose Analyzer will be maintained and operated according to the instructions in the manufacturer's operating manual.

Before the study begins, the YSI will be set up and appropriate maintenance will be performed. The YSI clock will be set to 24 hour format using an accurate time device, such as site central clock or atomic clock.

A set of four glucose control sera[3] that have been assayed by a method traceable to one proposed for use as a national glucose reference method developed through the combined efforts of the Center for Disease Control, the National Bureau of Standards, the American Association for Clinical Chemistry, and the FDA will be provided by Ascensia and used to verify the accuracy of the YSI Glucose Analyzer[4]. These controls will be run for pre-study and daily control tests, and will be within the lower and upper limits of the target levels noted in Table 5.1. The procedure for proper thawing and handling of the serum controls is found in Attachment 1.

Table 5.1: YSI serum control target values and limits, mg/dL

LOT#	LEVEL	TARGET	Lower Limit	Upper Limit
7AP204	2	49.1	46.6	51.6
7AP304	3	96.8	92.0	101.6
7AP404	4	193.5	183.8	203.2
7AP505	5	390.2	370.7	409.7

5.12.2 Pre Study and Daily Control Tests

These four glucose control sera will be used to verify the accuracy of each YSI analyzer before the study begins (Pre-study testing). Six (6) pre-study runs will be performed on each YSI that will be used in the trial: 2 runs per day for 3 days. The Ascensia Study Manager or designee will review the YSI pre-study glucose control data before the study begins.

The daily controls will be tested: 1 sip = 1 result from white probe and 1 result from black probe. Any YSI used on a given day to test subject blood samples will be monitored by assaying the 4 glucose controls at the beginning of the day. The YSI will be calibrated before each serum control sample is tested. The sequence of testing will be:

1. Calibrate the YSI
2. Test Control 2 (1 sip)
3. Calibrate
4. Test Control 3 (1 sip)
5. Calibrate
6. Test Control 4 (1 sip)
7. Calibrate
8. Test Control 5 (1 sip)

[3] Caution: The glucose traceability controls are human serum-based and must be handled using universal precautions.

[4] Neese J, Duncan P, Bayse D, *et al.* Development and evaluation of a hexokinase/glucose-6-phosphate dehydrogenase procedure for use as a national glucose reference method. HEW Publication No. (CDC) 77-8330. 1976. Atlanta, Centers for Disease Control.

Site staff will keep a maintenance log for each YSI, including daily operational checks, maintenance and membrane changes. A full set of serum controls should also be tested after YSI parts are changed (such as buffers, probes, or membranes).

5.12.3 Testing of Subject Plasma Samples

The subject plasma samples (capillary and venous) will be tested using 1 sip per test (=2 results, 1 from white and 1 from black probe) with calibration of the YSI before the first sip. A serum control (1 sip) will be tested after each subject plasma sample to verify the YSI Analyzer has remained in control during the plasma sample test. The control with target value close to the concentration of the subject plasma sample will be tested. The average of the black and white probe results will be verified to be within the ranges shown in Table 5.1.

If the control result is out of range, the YSI will be recalibrated and the control sample will be retested. If the control result is now within the appropriate range (Table 5.1), the control sample is confirmed as appropriate for use. The YSI analyzer will then be re-calibrated, the plasma will be re-tested, and the control will be tested per the protocol's plasma testing procedure already described.

If the control result is not within the appropriate range after the plasma sample has been tested twice, the results for this subject sample will be non-evaluable.

The sequence of testing for each subject sample will be:

1. Calibrate the YSI
2. Test plasma sample (1 sip)
3. Test control (1 sip)
4. Verify control result (mean of black and white probe results) is within limits in Table 5.1. If it is, stop and record result.
5. If not, repeat Steps 1, 3 and 4 to verify control sample is satisfactory for use.
6. When control result is shown to be within range in Table 5.1, repeat Steps 1-3.

If the control is again outside the limits, the results for this subject sample are non-evaluable.

Glucose values of the YSI replicates (both controls and plasma) should be within 4 mg/dL or 4% of each other (i.e. 4 mg/dL for values < 100 mg/dL and 4% for values ≥ 100 mg/dL). If they are not, an additional assay should be run.

5.12.4 Recording YSI Results

The YSI source documents will be labeled as follows throughout the study to facilitate matching glucose results on the source document with results recorded on the CRF:

Sample identification will include:

1) Ascensia serum traceability control level or
2) Subject ID plus either 'capillary' or 'venous' blood

NOTE: If glucose results are not to be used due to operator errors, insufficient sample, etc., this should be clearly marked on the YSI source document.

The YSI operator or designee will label all samples on YSI tape and record YSI results for all plasma and control sample runs on the appropriate source documents.

The YSI operator will record all non-numeric codes - QNS (Quantity not sufficient), NO (Not Obtainable), and error codes as appropriate for the YSI tests.

5.13 Subject Questionnaires

Site staff will administer two questionnaires to subjects. Questionnaire 1 will be given to all subjects and Questionnaire 2 will be given only to subjects with diabetes.

5.13.1 ***Questionnaire 1: Evaluation of Instructions for Use. (All subjects)***

Staff will administer a questionnaire to all subjects who perform fingerstick self-testing after the individual meter testing is completed.

The questionnaire will include statements for which a numerical score or rating will be provided by subjects (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree). These numerically scored statements will be tabulated into frequency distributions. The following statements will be subject to the pass/fail criteria listed in the study objectives section:

- I find it easy to do a fingerstick blood test with this meter.
- The meter display is easy to see and read.
- It was easy to understand my test results.
- The instructions (User Guide and Quick Reference Guide) were easy to understand.
- The instructions clearly explain how to run a test.
- The instructions clearly explain what to do if an error message is displayed by the meter. *Note: an error message will be demonstrated by the study staff if the subject does not experience an error message during his/her testing.*

Per ISO 15197:2013, Section 8.8.2, the questionnaire will also contain a section whereby the subject can provide unrestricted comments on their experience about using the BGMS. This questionnaire will be administered by the staff who will record the subject's responses. The subject will be given an example questionnaire to assist with providing the responses.

5.13.2 ***Questionnaire 2: BGMS Features. (Only subjects with diabetes)***

After all testing and the first questionnaire have been completed, the study staff will demonstrate to only the subjects with diabetes several features of the BGMS that would not necessarily be experienced during the brief accuracy testing. This will ensure that the subjects are able to understand the features, and answer questions in the questionnaire.

There are no acceptance criteria for this questionnaire. This questionnaire may be 1) administered by the staff who will record the subject's responses or 2) completed by the subjects and verified by the study staff, as per site procedures. In the first scenario, the subject will be given an example questionnaire to assist with providing the responses.

5.14 Procedures repeated on BGMS 2

After completing study procedures for the first BGMS randomly-assigned to them, subjects will then repeat all of these procedures using the second BGMS, except the hematocrit and venipuncture procedures. (Hematocrit is measured on a separate instrument and is not meter-

specific; venipuncture is performed once and measured on both meters, as previously described.) Therefore, for BGMS 2, subjects will complete a fingerstick test; a YSI sample will be collected by a Tenderlett stick from subject; subject will complete a palm AST; study staff will perform a fingerstick test from the subject; study staff will administer Questionnaire 1; and, if the subject has diabetes, study staff will administer Questionnaire 2.

Table 5.2 – Subject Testing Schematic

Step	BGMS	Test type	Operator	Description
1	1	Fingerstick Self-test	Subject	▪ Subject lances finger – Microlet NEXT lancing device. ▪ Test meter with 1 lot of test strip (Repeat 2 more times, only if needed). ▪ Record time of successful meter test.
2	1	Tenderlett deep stick	Study staff	▪ Immediately following Step 1 meter test (≤ 5 min), staff lances subject fingertip (up to 3 lancings allowed). ▪ Record time of lancing. ▪ Collect blood in Li Heparin tube (approx. 200 – 300 uL). ▪ Centrifuge blood and record time (should be within 15 min of meter test in step 1).
3	1	AST palm Self-test	Subject	▪ Immediately following Step 2, subject lances palm – Microlet NEXT lancing device. ▪ Test with same test strip lot and meter as above. (Repeat 2 more times, only if needed.) ▪ Record time of successful meter test (should be within 15 min of centrifugation in Step 2).
4	1	Study staff test	Study staff	▪ Immediately following Step 3, staff lances subject fingertip - Microlet NEXT lancing device. ▪ Test with same test strip lot and meter as above. (Repeat 2 more times, only if needed.) ▪ Record time of successful meter test (should be within 15 min of centrifugation in Step 2).
5	1 then 2	Venous test **(only subjects with diabetes)**	Study staff	▪ May be done prior to Steps 1-4. ▪ Staff performs venipuncture on subjects with diabetes (up to 3 attempts allowed). ▪ Collect blood in 4 ml Vacutainer tube with heparin anticoagulant. ▪ Staff tests blood (out of view of subject) with same meter and strip lot as fingerstick test. ▪ Centrifuge blood and record time (should be within 15 min of venous blood meter test).
6	na	Hematocrit	Study staff	▪ Fill 2 microhematocrit tubes (only 1 tube to be measured). ▪ Blood is from capillary or venous blood.
7	na	Questionnaire 1	Study staff	▪ Study staff administers Questionnaire 1 to all subjects.
8	na	Questionnaire 2 (**only subjects with diabetes**)	Study staff	▪ Study staff demonstrates BGMS features to subjects with diabetes. ▪ Study staff administers Questionnaire 2 to subjects with diabetes.
9-14	2	all	all	▪ Repeat steps 1 – 4 (meter tests) and 7-8 (questionnaires) with BGMS 2.

5.15 Device Problem Reporting

Any functional problems with the CONTOUR NEXT or CONTOUR TV3 BGMS will be documented by the study staff. The study staff should be specific about describing the problem and the sequence of events that led to it. All information will be documented on the Problem Reporter Form, including the meter type, serial number and test strip lot. Malfunctioning BGMs will be replaced and this will be documented for study tracking. If appropriate, such meters will be disinfected and shipped back to Ascensia for evaluation.

5.16 Temperature and Humidity Monitoring

The study staff will measure the temperature and humidity of the meter and YSI testing area(s) twice a day (AM and PM) using an audited thermometer/hygrometer supplied by Ascensia, and record the results on the appropriate form.

5.17 Miscellaneous

Ascensia representatives may observe subject visits as part of study staff training, study monitoring or for troubleshooting problems with the investigational devices. This will be done under supervision of the investigator.

Ascensia representatives may assist with disinfection of the meters, and perform centrifugation of blood samples and measurement of hematocrit.

Ascensia representatives will not train or interact in any way with the subjects. The presence of Ascensia representatives will be noted in the ICF.

Subjects will receive nominal compensation for their time and inconvenience.

6.0 Risk / Benefit Assessment

Risks associated with this study include those associated with obtaining blood from finger, palm and venipuncture.

The following risks are anticipated and will not be reported as Adverse Events (AE). (See section 7.0 for further details.)

1) Bleeding: Mild bleeding similar to being stuck with a pin
2) Swelling (Edema): A mild swelling similar to a mosquito bite
3) Bruising: Less than one inch across (fingerstick) or less than 2 inches across (venipuncture)
4) Redness (Erythema): Mild reddening or darkening of the skin in the immediate area around the puncture site
5) Soreness: Mild discomfort at the puncture site resolving (going away) within one to two days (fingerstick or palm) or within hours (venipuncture)

The following risks are unlikely, but possible, and will be reported as anticipated Adverse Events:

1) Bleeding: Continued bleeding requiring changing a bandage
2) Bruising: A worsening bruise that is firm to the touch

3) Redness (Erythema): Bright redness or skin darkening spreading across the area (fingerstick or palm) or across the arm (venipuncture)
4) Soreness: Worsening pain and/or pain that interferes with activity
5) Infection: Bright redness or skin darkening spreading across the area with warmness and/or swelling, and/or red streaking
6) Nerve injury: Numbness or shooting pain in the forearm
7) Numbness in the area of the puncture wound
8) Dizziness
9) Fainting

Subjects should be instructed to report such events to the investigator or designee.

Benefits

A benefit associated with the study is the sense of well-being gained by contributing to the development of improved or new blood glucose monitoring systems, which may be beneficial to people with diabetes or other diseases or conditions.

7.0 Adverse Event Management and Medical Device Reporting

The procedures to be performed under this protocol are considered to be low risk.

7.1 Description and Classification

7.1.1. An AE during a clinical evaluation is "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device." It is not dependent on whether the event is considered to be related to the investigational product or the study. An AE includes events not seen at the beginning of the study, or worsened if present at the beginning. Adverse events can be classified as presented in Table 7.1.

7.1.2. The next classification to consider is whether or not the AE is Anticipated or Unanticipated. In order for an AE to be considered 'anticipated' it must be listed in the protocol and ICF prior to any occurrence.

7.1.3. For studies on products that have not yet been cleared for market, it is important that all AEs be documented and included in the study file.

7.1.4. An unanticipated adverse device effect (UADE) is: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects [21CFR812.3(s)].

7.1.5. All AEs observed by the Investigator or reported by the subject will be documented on the AE form (including all symptoms) and included in the study file.

7.2 Events related to hypoglycemia and hyperglycemia

Hypoglycemia and hyperglycemia can be a common occurrence with subjects who have diabetes.

If it is found that a subject has a hypoglycemic event, as determined by the Principal Investigator (PI) during a study visit, the subject will be treated by the site staff accordingly. Appendices D and E note each site's treatment plan.

Classification of the hypoglycemic or hyperglycemic event is at the discretion of the PI or designee. If the hypoglycemic or hyperglycemic event is considered by the PI as an AE, it will be considered to be an anticipated AE and will be recorded on the AE Form.

Subjects who are hypo- or hyperglycemic may continue with fingerstick testing if they so choose, and if the PI determines that it is safe. The PI will define what is considered to be a hypoglycemic or hyperglycemic state.

Table 7.1: Classification of Adverse Event

Serious*	Non-Serious
An adverse event that leads to: a) death; b) a serious deterioration in health of the subject that, 1) resulted in a life-threatening illness or injury, 2) resulted in a permanent impairment of a body structure or a body function, 3) required in-patient hospitalization or prolongation of existing hospitalization, 4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function; c) fetal distress or a congenital abnormality or birth defect. May be anticipated or unanticipated. **EN ISO 14155. Clinical investigation of medical devices for human subjects – Good Clinical Practice*	All adverse events not reported as serious. At each visit, all adverse events observed by the investigator/designate or reported by subject must be evaluated and recorded on an adverse event form. A non-serious adverse event is further classified with respect to severity and relationship to the trial product. A non-serious adverse event may be anticipated or unanticipated. Further classification with regard to severity • Mild: Transient symptoms, easily tolerated, no interference with subjects daily activities. • Moderate: Marked symptoms, moderate interference with subjects daily activities, and tolerable. • Severe: Considerable interference with subject's daily activities, not tolerable.
Relationship to trial product: • Definitely Related: Causal relationship has been established and documented • Probably Related: Good reasons and sufficient documentation to assume causal relationship have been established • Possibly Related: Causal relationship is likely and cannot be excluded • Probably Not Related: Good reasons and sufficient documentation not established to assume causal relationship • Not Related: The event is most likely related to an etiology other than the trial treatment	

7.3 Procedure for Reporting an Adverse Event

Adverse events will be documented during this study by completing the AE Form. During the visit, AEs will be evaluated by a member of the study staff. The nature of each event and date of onset, outcome, course, maximum intensity and action taken with respect to treatment should be established. Details of any corrective treatment should be recorded on the AE Form. Investigators should follow-up on the status of subjects experiencing an ongoing AE until the event has been resolved, or until the condition has stabilized.

7.3.1. The Investigator or designee will notify the Study Manager or Monitor within 24 hours of any Serious Adverse Event that occurred during the study. The sponsor will promptly review all information relevant to the safety of the investigational device.

7.3.2. The investigator or designee must notify the sponsor and reviewing IRB by phone or fax of Unanticipated Serious Device-Related Adverse Events within 24 hours of learning of the event, followed by a written a report within 10 working days after learning of the event.

7.3.3. Upon receipt of a report of an UADE by the Ascensia Study Manager or Monitor, the report will be immediately forwarded to:

Andreas Stuhr, MD

Ascensia Director of Medical and Scientific Affairs

[redacted]

7.3.4. The sponsor (Ascensia) must report UADEs to the FDA, all participating investigators, and reviewing IRBs within 10 working days after the sponsor first receives notice of the event.

7.3.5. Regardless of the above definitions, any additional adverse experience that the investigator considers serious, and/or of concern in relationship to the study must be documented and reported to the Study Manager or Monitor within 24 hours.

7.4 Medical Device Reporting

The Microlet NEXT lancing device system is an Ascensia-marketed product in the US. If an AE occurs that is directly caused by the marketed product, the AE should be reported immediately, but in any case within 24 hours, to the Customer Service Department at 1-800-348-8100. Also contact the Ascensia representative listed in Section 12.0.

8.0 Study Termination and Subject Withdrawal Criteria

8.1 Criteria to Withdraw / Discontinue a Subject from Study

Subjects may be withdrawn from the study at their own request for any reason, or at the discretion of the PI (or designee) for one of the following reasons:

1) Adverse Event
2) Illness of a subject
3) Subject non-compliance with protocol requirements
4) Other, at the discretion of the investigator

In such cases, the subject will be withdrawn from further study participation. Data collected from withdrawn subjects will be analyzed and results will be retained for safety assessments. If available, data will be retained in analyses related to the primary objective of the study unless there is a valid reason to believe that the data may be biased, incorrect, or confounded.

9.0 Regulatory

9.1 Regulatory Status of the Investigational Devices

In addition to the regulations outlined in the Ascensia Diabetes Care Global Clinical Affairs standard operating procedures, this protocol also complies with the clinical trial regulations of British Standard BS EN 13612:2002, "Performance evaluation of in vitro diagnostic medical devices."

9.2 Investigational Review Board (IRB) Approval

Prior to study initiation, an IRB must review this protocol, the ICF, and any other supporting study documents which impact subject safety. The investigational site may not begin the study until the IRB has given its written and dated approval via a letter that identifies the version/date of the protocol and ICF. A copy of the IRB approval letter and approved ICF must be provided to the Investigator and to Ascensia prior to the Study Initiation Visit.

9.3 Informed Consent Requirement

Each subject must provide informed consent before she/he can participate in the study. The informed consent process fully apprises the subjects of the risks and benefits to them and to society for participating in the study. The ICF will clearly state that designated study personnel will be able to view the subject's medical records. The ICF will also state that Ascensia representatives may observe some subjects as part of study staff training, study monitoring or for troubleshooting problems with the investigational devices.

If the subject understands and agrees to participate in the study, she/he will sign the ICF. All subjects will be given a copy of the ICF. If a subject has a question about his/her rights, he/she may contact a member of the IRB at any time during or after study participation.

9.4 Study Documentation Procedures

The investigator will keep study records for a minimum of three years. Alternatively, other arrangements may be made with Ascensia for study document storage.

9.5 Study Monitoring

The study will be monitored by Ascensia representatives. A monitoring plan will be completed by the Study Manager/designee prior to the study. The Study Manager or designee will conduct a study initiation visit, at least 1 monitoring visit, and a close-out visit. Note: the latter two visits may occur within a continuous timeframe.

Ascensia representatives may observe some subject visits as part of study monitoring. This will be done under supervision of the investigator. Ascensia representatives will maintain subject confidentiality and will not interfere with rights of human subjects, safety or bias study conduct.

9.6 Investigator's Report of Study Closure

Ascensia representatives will send a letter to the site informing them that the study is closed. The study will be considered closed when the data has been locked for data analysis.

The Investigator or designee will submit a report summarizing subject disposition and other study details, as appropriate, to the Ascensia Study Manager and the reviewing IRB. This report will be completed within 3 months of the study closure date.

In addition, the Ascensia Study Manager, or designee, will report the completion of the study to the IRB within 6 months of study closure.

9.7 Registration of Trial

The clinical trial will be registered with www.clinicaltrials.gov as required.

9.8 Clinical Study Reports (CSR)

Four CSRs will be written by the sponsor. Two CSRs will be written for CONTOUR NEXT: one report will evaluate data according to ISO 15197:2013 criteria and one report according to FDA SMBG:2016 criteria. Two CSRs will be written for CONTOUR TV3: one report will evaluate data according to ISO 15197:2013 criteria and one report according to FDA SMBG:2016 criteria.

10.0 Data Collection and Management

A unique number will identify each subject. The unique number will be the only identifying information entered. A master list of subject names, with their subject IDs, will be kept by the Investigator at the study site. The Investigator will retain all signed IC documents.

Clinical data will be primarily collected through an EDC system used by Ascensia. Study data will be recorded on forms that will serve as source documents for the EDC system. These original Forms will be retained by the site.

In addition to data collection, the EDC system will be used for data cleaning as well as monitoring operations. Site and sponsor users will be trained on the system prior to the study start, and their access to EDC system will be contingent upon successful completion of training requirements. Study personnel will complete and sign all appropriate source document forms in compliance with Good Clinical Practice (GCP). Source documents (Forms) should be completed legibly, in black or blue ink. If it is necessary to make corrections, a single line should be drawn through the original entry, the new entry written in, and the correction initialed and dated by the individual making the correction.

The original forms will be retained by the Investigator for a minimum of three years.

The Investigator or designee will sign and date an AE Form for each AE experienced by any subject.

YSI source documents (tapes) will be photocopied to preserve the image on the thermal paper. Site staff or designees who photocopy the YSI tapes will certify (with signature, date, and YSI ID) that the copy is a true and accurate representation of the original.

11.0 Data Analysis

The following analyses apply to both CONTOUR NEXT and CONTOUR TV3 meters, with analyses for each meter independent of the other.

11.1 Accuracy Objectives

Primary Objective – Accuracy with All Subjects Included

Let MeterBG = meter blood glucose result;

LabBG = laboratory method (YSI) comparator blood glucose result.

For the primary accuracy objective, a result (MeterBG) is considered accurate if:

$$|RD| = 100*|MeterBG - LabBG| / LabBG \leq 15\%, \text{ regardless of the value of LabBG.}$$

With n = 350 evaluable results, *Xc* = 333 results would be required to satisfy the accuracy criteria. At P_0 = 96.65%, there is approximately a 95% chance of satisfying the primary objective. Conversely, at P_a = 92.81%, there is approximately a 95% chance of failing to satisfy this accuracy objective.

In addition to the ±15% accuracy definition, at least 99% of the n = 350 fingerstick results must satisfy:

$$|RD| = 100*|MeterBG - LabBG| / LabBG \leq 20\%, \text{ regardless of the value of LabBG.}$$

Thus at least 347 out of n = 350 results must satisfy the ±20% accuracy definition.

With n = 350 evaluable results, *Xc* = 347 results would be required to satisfy the accuracy criteria. At P_0 = 99.61%, there is approximately a 95% chance of satisfying this objective. Conversely, at P_a = 97.80%, there is approximately a 95% chance of failing to satisfy this accuracy objective.

Secondary Objectives

Assume 315 evaluable results from people with diabetes. The ISO 15197:2013 acceptance criterion is that 95% of those evaluable results must satisfy the accuracy criteria:

$|D| = |MeterBG - LabBG| \leq 15$ mg/dL, for LabBG < 100 mg/dL

or

$|RD| = 100*|MeterBG - LabBG| / LabBG \leq 15\%$, for LabBG ≥ 100 mg/dL.

With n = 315, Xc = 300 results would be required to satisfy the accuracy criteria. At P_0 = 96.79%, there is approximately a 95% chance of satisfying the primary objective. Conversely, at P_a = 92.77%, there is approximately a 95% chance of failing to satisfy this objective.

Secondary Objective –Internal Requirements

1. ±10.5% or ±10.5mg/dL (CONTOUR NEXT)

The hypothesis:

H_0: Pr{|RD| ≤ 10.5% when YSI ≥ 100mg/dL or |D| ≤ 10.5mg/dL when YSI < 100mg/dL} < 0.95

Will be tested against the alternative:

H_1: Pr{|RD| ≤ 10.5% when YSI ≥ 100mg/dL or |D| ≤ 10.5mg/dL when YSI < 100mg/dL} ≥ 0.95

With n = 315, the critical number of "successes" is Xc = 294. That is, at least 294 out of n = 315 results must satisfy the requirement:

|RD| ≤ 10.5% when YSI ≥ 100mg/dL or |D| ≤ 10.5mg/dL when YSI < 100mg/dL

This acceptance criterion (critical value) gives about a 92.62% chance of rejecting H_0 in favor of H_1 if the actual probability of "success" is 0.95.

2. ±12.5% or ±12.5mg/dL (CONTOUR TV3)

The hypothesis:

H_0: Pr{|RD| ≤ 12.5% when YSI ≥ 100mg/dL or |D| ≤ 12.5mg/dL when YSI < 100mg/dL} < 0.95

Will be tested against the alternative:

H_1: Pr{|RD| ≤ 12.5% when YSI ≥ 100mg/dL or |D| ≤ 12.5mg/dL when YSI < 100mg/dL} ≥ 0.95

With n = 315, the critical number of "successes" is Xc = 294. That is, at least 294 out of n = 315 results must satisfy the requirement:

|RD| ≤ 12.5% when YSI ≥ 100mg/dL or |D| ≤ 12.5mg/dL when YSI < 100mg/dL

This acceptance criterion (critical value) gives about a 92.62% chance of rejecting H_0 in favor of H_1 if the actual probability of "success" is 0.95.

3. Study Staff Test

Two tests of the hypotheses will be performed.

The hypothesis:

H_0: Pr{|RD| ≤ 15% when YSI ≥ 100mg/dL or |D| ≤ 15mg/dL when YSI < 100mg/dL} < 0.95

will be tested against the alternative:

H_1: Pr{|RD| ≤ 15% when YSI ≥ 100mg/dL or |D| ≤ 15mg/dL when YSI < 100mg/dL} ≥ 0.95

One test will be done using data from all subjects, and another using data only from PWD subjects. In the case of all subjects, if n = 350, the critical value is 327. For PWD subjects only, if n = 315, the critical value is 294. As in all cases, critical values may require adjustment due to differences in sample sizes. The critical values are chosen so that the least upper bound on the probability of passing under minimally acceptable conditions is 95%.

Table 11.1 summarizes critical values for satisfying objectives described in section 2. The column labeled P_o is the minimally acceptable condition (probability) for each objective listed.

Table 11.1 Sample Sizes and Critical Values for Satisfying Objectives

Objective	Sample Size, n	Critical Value, Xc	Po	Derivation of Critical Value*
2.1.1(95%), 2.2.1	350	333	96.65%	95% of n
2.1.1(9%)	350	347	99.61%	99% of n
2.3.1, 2.3.2, 2.3.3	315	300	96.79%	Pr{PASS|Xc,Po} ≈ 95%
2.4.1	315	294	95.00%	Pr{PASS|Xc,Po} ≈ 95%
2.4.2 (all subjects)	350	327	95.00%	Pr{PASS|Xc,Po} ≈ 95%
2.4.2 (PWDs)	315	294	95.00%	Pr{PASS|Xc,Po} ≈ 95%
2.2.2 (Questionnaire 1, All Subjects)	350	307	90.00%	Pr{PASS|Xc,Po} ≈ 95%
2.3.4 (Questionnaire 1, PWDs)	315	276	90.00%	Pr{PASS|Xc,Po} ≈ 95%
*Critical Values may change depending on actual sample size				

Note that error distribution tables will be constructed, to reflect the numbers and percentages of results falling within various error ranges (e.g., ±5%, ±7%, ±10%, ±12.5%, ±15%, ±20%). Tables will be by clinical site and overall.

11.2 Other Statistical Computations

Some data analysis follows analyses and presentations described in ISO Section 15197:2013, Section 8. See Table 11.2 for scheme of data analysis, including capillary fingerstick blood and venous blood.

Other data analysis follows analyses and presentations described in the FDA SMBG: 2016. See Table 11.3 for scheme of data analysis, including capillary fingerstick blood and venous blood per the FDA SMBG:2016.

Linear regression will be performed on data comparisons as shown in Tables 11.2 and 11.3.

Modified Bland-Altman Plots – Modified Bland-Altman plots (difference between evaluation device results and reference results plotted against reference results) will be constructed for all comparisons described in Tables 11.2 and 11.3.

Confidence Intervals

Confidence intervals (95%, two-sided) for all primary and secondary objective proportions (percents) will be computed using the Clopper-Pearson[5] (1934) formula:

$$P_L = \frac{X * F^{-1}_{\alpha/2}(2X, 2(n-X+1))}{n-X+1+X * F^{-1}_{\alpha/2}(2X, 2(n-X+1))}$$

and:

$$P_U = \frac{X * F^{-1}_{1-\alpha/2}(2X, 2(n-X+1))}{n-X+1+X * F^{-1}_{1-\alpha/2}(2X, 2(n-X+1))}$$

P_L = lower limit

P_U = upper limit

X = number of "accurate" results (per the relevant definition of "accurate")

Regression and Outlier Analysis

A linear regression of the BGMS results against the YSI reference method results via weighted least squares (WLS) will be performed, with weights:

$w = \frac{1}{YSI^2}$ used to account for the proportional variance nature of blood glucose measurements (Draper and Smith, 1998)[6].

Studentized residuals from the regression will be computed, i.e.,

$$e_i = y_i - \hat{y}_i$$

[5] Clopper, C.J., Pearson, E.S. (1934) The use of confidence or fiducial limits as illustrated in the case of the binomial, Biometrika, 26, 404-413

[6] Draper, N. R., Smith, H., (1998) Applied Regression Analysis, 3rd Ed., John Wiley and Sons

$$\varepsilon_i = \frac{e_i}{s_\varepsilon}$$

That is, a studentized residual, ε, is the residual, e, divided by the standard error of residuals, s_ε

$$s_{\varepsilon_i} = \hat{\sigma}\sqrt{1 - h_{ii}}$$

$\hat{\sigma}$ = root mean square error (RMSE) from the regression model.

and h_{ii} is the leverage for the i^{th} observation.

A BGMS result will be considered an "outlier" if its corresponding studentized residual is outside the interval $(\Phi^{-1}(0.005), \Phi^{-1}(0.995)) \approx$ (-2.576, +2.576), corresponding to a 99% interval for a standard normal variate. By this statistical definition of "outlier", results that may satisfy accuracy requirements may be considered "outliers".

Confidence bands (95% and 99%) for the regression line will be computed. Scatter plots of MeterBG vs. LabBG will be constructed, with the regression line, the confidence bands, and the line of identity (Y = X) will all be plotted. Outliers will be identified.

Error Grid Analyses

Parkes consensus error grids will be constructed for combined strip lots, and combined sites as described in Tables 11.2 and 11.3. There are no criteria for percentages of values within the error grid zones.

Data Analysis Schemes

Table 11.2 Data Analysis Scheme (per ISO 15197:2013)

Blood Type	Data Comparison	Regression Tables	Bland Altman Plots	Accuracy	Error Grid	Error Interval tables (5, 10, 12.5, 15, 20, >20%)
Capillary Fingerstick	Subject vs. YSI	x*	x***	x**	x*	x*
	Staff vs YSI	x*	x***	x**	x*	x*
AST (Palm)	Subject vs. YSI	x*	x***	x**	x*	x*
Venous	Results vs. YSI	x*	x***	x**	x*	x*

* Combined sites

** By site and combined sites

*** Plots with different symbols denoting the site, and whether observations are outliers

Table 11.3 Data Analysis Scheme (per FDA SMBG: 2016)

Blood Type	Data Comparison	Regression Tables	Scatter Plots	Accuracy	Error Grid	Error Interval tables (5%, 7%, 10%, 15%, 20, >20%)
Capillary Fingerstick	Subject vs. YSI	x*	x***	x**	x*	x*
	Staff vs YSI	x*	x***	x**	x*	x*
AST (Palm)	Subject vs. YSI	x*	x***	x**	x*	x*

* Combined sites

** By site and combined sites

*** Plots with different symbols denoting the site, and whether observations are outliers

Note: Samples outside +/- 20% will be identified and listed in the statistics report (per FDA SMBG: 2016).

11.3 Subject Questionnaires 1 and 2

Subject questionnaires 1 and 2 will consist in part of questions/statements for which a numerical score or rating (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree) will be provided by the subjects and entered by the study staff. For these numerically-scored questions, frequency distributions will be tabulated.

For Questionnaire 1 only:

Hypothesis tests for selected statements will be performed. The hypotheses are:

$$H_0: Pr\{response \geq 3\} < 90\% \text{ versus the alternative:}$$

$$H_a: Pr\{response \geq 3\} \geq 90\%$$

The critical number of responses greater than or equal to 3, Xc, is a function of the actual sample size, and will be chosen such that $0.95 = sup\ Pr\{X \geq X_c | 100p\% = 90\%\}$. For example, if n = 350, then Xc = 307, so that $Pr\{X \geq X_c | 100p\% = 90\%\} \approx 0.9316 \leq 0.95$. That is, 307 is the number of responses ≥ 3 which yields the largest value of $Pr\ \{X \geq X_c | 100p\% = 90\%\} \leq 0.95$ for n = 350. For n = 315, the critical value is Xc = 300 (power ≈ 0.95).

11.4 Demographic, Diabetes History, Medications and Medical Conditions Data, Questionnaires 1 and 2

Descriptive statistics for Demographics, Diabetes History, Medications and Medical Conditions, and subject questionnaires will be computed as appropriate. Histograms will be constructed where appropriate. A percentage of subjects < 65 years of age will be calculated.

11.5 Hematocrit Analysis

Hematocrit will be measured in singlet for each subject. Subjects with a hematocrit determination that is out of range cannot be used for blood glucose measurement comparisons.

Subject hematocrit measurement should be within 0-70% in order for the subject BG results to be considered evaluable for the ISO 15197 analysis. For the analysis according to the FDA SMBG: 2016, all subjects will be considered evaluable.

The mean, median, minimum, maximum, and standard deviation, will be computed for hematocrit determinations, for subjects with diabetes and for all subjects, by site and for both sites combined.

11.6 Temperature and Humidity

Means, medians, standard deviations, minimum and maximum room temperatures and humidities will be computed by site and for both sites combined.

11.7 Glucose distribution

The distribution of YSI glucose and a histogram (combined sites) for both capillary and venous blood will be provided. The mean, median, minimum, maximum, and standard deviation will be computed for glucose distributions, for subjects with diabetes and for all subjects, by site and for both sites combined.

In addition, the number of capillary samples with concentrations <80 and > 250 mg/dL will be reported.

11.8 Data Listing

A listing of the data (excel sheet) is needed for the CSR. The listing should include: subject and staff fingerstick meter results, AST (palm) meter results, venous meter results, capillary and venous mean YSI results, subject ID, hematocrit.

A listing of subject comments including subject IDs from the Ease of Use Questionnaire is needed for the CSR.

Note: If supplemental or unplanned analyses are requested, they will be presented in a supplemental report.

12.0 Administration

All investigator and site staff communications regarding the study should be directed to the Ascensia Study Manager. Please contact the Ascensia Study Manager noted below for any questions or problems concerning the clinical trial.

Documents to be collected prior to the start of the study include, but are not limited to:

1) CVs of Investigator and Sub-Investigators
2) Signature of PI on page 2 of protocol
3) IRB approval letter
4) IRB-approved ICF
5) Financial Disclosures for PI and Sub- Investigators
6) Clinical Trials Agreement (including Investigator Agreements for PIs and Sub-Investigators)
7) Site staff GCP training documentation

Data / documents to be collected during or after completion of the study include, but are not limited to:

1) EDC database
2) Progress Notes
3) Signature and Delegation Log (for all study staff)
4) Investigator's Report of Study Closure and IRB acknowledgement
5) Study-related training documentation

Appendix A - Instructions for Cleaning and Disinfecting Meters

Single-use items, such as test strips, test strip vials or lancing devices, shall not be used with multiple subjects and will be discarded in biohazardous containers after use. Blood glucose meters will be single-use, and will be cleaned and disinfected before returning to Ascensia by study staff only. Study staff will disinfect meters using the EPA-registered disinfectant noted in the UG and below that is suitable for use on hard, non-porous surfaces. Ascensia will provide the disinfectant.

EPA Registration	Manufacturer	Product Name	Active Ingredient
67619-12	Clorox Professional Products Company	Clorox Bleach Germicidal Wipes	0.55% sodium hypochlorite

1. Follow the manufacturer's directions printed on the container. Wear gloves.
2. If the meter is soiled, clean until all soil is removed before disinfecting.
3. Disinfect by wiping the meter with the disinfectant wipe until wet, and continue wiping for 60 seconds. Take care to prevent solution from running into the test strip port or around the buttons.
4. Dry the meter with a clean paper towel.
5. Dispose of all materials used in the cleaning and disinfecting procedure according to current lab biohazard procedures.

References

Protection of laboratory workers from occupationally acquired infections; approved guideline – third edition. CLSI document M29-A3. ISBN1-56238-567-4.

Rutala W, Weber D, Healthcare Infection Control Practices Advisory Committee. Guideline for disinfection and sterilization in healthcare facilities, 2008. CDC.

FDA, Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling, May 2, 2011.

Appendix B - Instructions for Collection/Processing of Blood for YSI

Capillary Blood Collection

1. The study staff will perform a deep finger puncture using a Tenderlett, or similar, lancing device, on the subject's finger.
2. The study staff will express the blood and collect approximately 200 - 300 µL in a blood collection tube (e.g. BD Microtainer with lithium heparin). A hand warmer may be used to improve blood flow and facilitate sample collection. Detailed instructions are as follows:
   - Typically the best finger to choose is the middle finger. It is recommended to practice the finger massaging technique prior to puncture.
   - Give subject a hand-warmer to hold for several minutes prior to puncture. Note that the hand-warmer should be moved to the subject's wrist when ready for puncture and kept there during the whole collection procedure.
   - Angle finger with tip slightly downward and squeeze fingertip gently prior to puncture.
   - Consider placement of finger puncture device: Choose a puncture site that will allow you to use your dominant hand to collect the blood. The device should be aligned so that the opening (where the blade comes out) is perpendicular to the grooves of the fingerprint and so that the opening is placed to the side of the finger (not too close to the nail).
   - While continuing to hold the fingertip, squeeze firmly, hold device firmly against side of finger and trigger the blade. Then turn the finger so that the nail is facing up.
   - Remove pressure from fingertip (to allow capillaries to fill with blood) and collect the first drop.
   - Begin massaging motion – continuous message of sides of the finger – this is critical.
   - Continue massaging finger from base to tip as you continue to collect the blood drops into the tube. If blood flow reduces it may help to press on the nail a bit in between massaging the finger. Having the subject stand up and drop their hand may also help.

Processing of Capillary or Venous Blood for YSI Analysis

1. Once collected, process the microtainer tube for laboratory glucose analysis as follows:
   - Label all tubes with the subject number and a C or a V (Capillary or Venous) as appropriate using a Sharpie marker. Also include a pre-determined notation for the capillary samples as to which meter test the sample corresponds (CONTOUR NEXT or CONTOUR TV3).
   - Gently invert the microtainer tube several times to mix the anticoagulant.
   - Centrifuge the whole blood immediately to separate the plasma from the red blood cells. Centrifugation must occur within 15 minutes of first meter blood test. Timing of all meter testing/centrifugation will be recorded on the appropriate CRF.
   - It is recommended that after centrifugation, the plasma is transferred from the microtainer tube to a micro/dispo tube or similar container. Ensure the container is labeled and the cap is secured.
   - The capped plasma sample may be kept at room temperature for up to 4 hours before testing.

2. If testing on the YSI Analyzer is not completed within 4 hours of sample collection, the plasma should be refrigerated for up to 24 hours, after which it should be frozen until the sample is tested.
3. Shipment of samples to Ascensia for glucose determinations may be recommended if YSI Analyzers do not meet the accuracy guidelines for the Ascensia traceability control sera. Arrangements will be made to ship the samples with dry ice via prepaid express mail should it become necessary.
4. Glucose values of the YSI replicates (controls and plasma) should be within 4 mg/dL or 4% of each other; if not, an additional assay should be run.
5. Insufficient (or suspected to be insufficient) samples, missing samples, and other sample issues should be recorded in the CRF and on the YSI printout as appropriate. If a sample is hemolyzed, record in the CRF.

Appendix C - Instructions for Hematocrit Sample Preparation & Testing

Staff performing the hematocrit will be trained in this procedure during the initiation visit by the study manager or designee.

1. Two hematocrit tubes will be obtained from each subject's blood. One tube will be measured and the result recorded on the form. The second tube will be measured only if the first tube was not adequate for measurement. Note:
   - Sample that is collected from venous blood will be collected in **un-treated micro-hematocrit tubes**.
   - Samples collected from capillary fingerstick blood will be collected in **treated micro-hematocrit tubes.**
2. Place a microhematocrit tube against the surface of the blood drop. Do not place the opening of the tube flush against the skin or it will be occluded.
3. Fill the microhematocrit tube about halfway. Do not over-fill. Then immediately place one of the microhematocrit tube openings in the clay sealant. Press into the clay 2-3 times to make sure enough sealant is transferred.
4. Place the sealed microhematocrit tube into the micro-centrifuge. Note: it is very important to place the microhematocrit tube in centrifuge rotor with clay side pointed outward. Spin for approx. 2 mins. Use dialed setting on StatSpin centrifuge.
5. Reading of hematocrit using StatSpin Crit-reader
   - After collection and centrifugation of hematocrit, place tube rotor in StatSpin Crit-reader, with clay side to the right.
   - Slide the marker on the crit-reader to the exact line where the clay and red blood cells meet (this is the "0" line). Press set button until "0" shows in the display.
   - Then move marker all the way over to the other end of the tube to the exact line where the plasma ends – press the set button until "100" shows in the display.
   - Now you are ready to read the hematocrit result. Slide the marker to the exact line where the red blood cells meet the plasma.
   - The result in the display is the hematocrit percentage for that sample.
6. An alternative to Step 5 is manual reading of the hematocrit by the operator using Manual **S**tatSpin Micro Hematocrit Capillary Tube Reader.
7. Record hematocrit result on the appropriate form.

Appendix D - Hypoglycemia Protocol at AMCR Institute

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Timothy S. Bailey, MD, CPI

Director

Hypoglycemia Protocol

I. **Objective:** To promptly reverse hypoglycemia in a consistent and therapeutically appropriate manner.

II. **Definition**: Hypoglycemia is a blood glucose that is <= 70 mg/dl even in the absence of obvious signs and symptoms. Signs and symptoms that may suggest hypoglycemia include: Shaky, sweaty, altered state of consciousness or personality change. The subject may report "I feel hypoglycemic".

III. **Procedure:**

A: Concious Patient without IV access in place:

1. Report all hypoglycemia to the supervising investigator immediately.

2. Treat with 15 gm of simple CHO. (Choose one)

- Three or four Glucose tablets (preferred choice.)
- 3/4 cup (6oz) of fruit juice (no sugar added)
- 3/4 cup (6ox) of non-diet soda (Coke, Pepsi, 7-Up, etc.)
- 1 cup of skim milk.

3. Repeat the blood glucose in 20 minutes and document. Notify the supervising investigator.

4. If the glucose is < 70 mg/dl after treatment.

- Repeat 15 gm of simple carbohydrate.
- Continue to perform blood glucose every 20 minutes and document results.
- Continue to administer 15gm of simple carbohydrates every 20 minutes until the blood glucose is over 60 or until directed otherwise by the supervising investigator.

AMCR Institute SOP – Hypoglycemia Protocol

Approved: 1 December 2010 by Timothy Bailey, MD

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Timothy S. Bailey, MD, CPI

Director

B. For all patients with IV access whether eating or NPO.

1. Treat with D50 if glucose is < 60 mg/dL. To determine the dose use this formula:

(100 – BG) x 0.3 = Number of ml of D50W to push.

2. Notify the supervising investigator of the results.

3. Repeat the blood glucose 20 minutes after the treatment is provided and document results.

4. If the blood glucose is less than 60 mg/dl, repeat the D50 using the same dosing formula with the most recent glucose result.

C. Unconscious patients without IV access:

1. Treat with 1mg of Glucagon (adult dosage) IM or SQ. Notify the supervising investigator.

2. Patients receiving Glucagon may experience nausea and vomiting. It is imperative to turn the patient on their side during treatment to avoid aspiration.

3. Establish IV access and await further orders from the supervising investigator.

4. Repeat the blood glucose (BG) 20 minutes after the Glucagon dose to measure the drug's effectiveness and patient response to the medication.

IV**. Documentation:**

A. Document the administration of glucose tablets, juice, Glucagon, and D50 in the study chart

AMCR Institute SOP – Hypoglycemia Protocol

Approved: 1 December 2010 by Timothy Bailey, MD

Appendix E - Hypoglycemia Protocol at Rainier Clinical Research Center

Rainier Clinical Research Center
HYPOGLYCEMIA ACTION PLAN

CLINICAL CONDITION	HYPOGLYCEMIA ACTION PLAN
• Blood glucose <70 mg/dL, but ≥50 mg/dL • With or without symptoms	• Treat if patient exhibits neuroglycopenic symptoms, patient requests or investigator discretion • No treatment if asymptomatic. If blood glucose has not increased to ≥70 mg/dL after 2 hours, then treat. • Treat hypoglycemia with glucose tabs: 16 grams initially, with repeat treatment every 15-20 minutes at discretion of investigator until blood glucose is increasing or blood glucose ≥100 mg/dL
• Blood glucose <50 mg/dL • With or without symptoms • Subject able to self-administer glucose tabs	• Treat hypoglycemia with glucose tabs: 16-32 grams (amount at investigator discretion) initially , with repeat treatment every 15-20 minutes at discretion of investigator until blood glucose is increasing or blood glucose ≥100 mg/dL
• Blood glucose <50 mg/dL • Subject is NOT able to self-administer glucose tabs	Severe hypoglycemia (defined as a hypoglycemic event requiring assistance of another individual to actively administer treatment) • Treat hypoglycemia with 1 mg intramuscular glucagon or intravenous glucose 20cc of 50% glucose • Monitor vital signs and blood glucose until glucose returns to normal range and patient regains full consciousness • If on an insulin pump, suspend insulin delivery until glucose is ≥70 mg/dL • Transfer to acute care facility at discretion of the investigator

Rev. 1/31/18

Attachment 1: Proper Handling of Ascensia YSI Serum Controls

Ascensia R&D completed characterization of six-level serum controls purchased from Bio-Techne® (formerly Bionostics). During the characterization, staff observed that sample stratification during thawing can occur if the control vials are not handled judiciously. The recommended procedure is as follows.

1. Thaw the frozen control amber glass vials at 2-8ºC for 2-3 days in the refrigerator. Each vial holds approximately 2.0 mL.
2. Before opening, mix the vials well by gently inverting them at least 10 times.
3. Prepare an aliquot of each level in capped microcentrifuge tubes. Cap tightly. We prefer Fisherbrand™ Microcentrifuge 0.5mL tubes (PN 02-681-333) with O-ring seal caps (PN 02-681-358).
4. Store any remaining control in the amber glass vials at 2-8ºC.
5. Before running a control sample on the YSI, mix the aliquot tubes by gently inverting them.
6. At the beginning of each day, remix the amber glass vials and refill the aliquot tubes. When not in use, store the aliquots at 2-8ºC.
7. The thawed control use life is two weeks. Discard all thawed control—aliquot tubes and amber glass vials—after two weeks.
8. Since slow thawing for 2-3 days is recommended, it is advisable to keep an extra thawed set available for testing.